Basis for the Amendments

Claims 16, 17, 22 and 23 have been canceled without prejudice and without any intention to abandon the subject matter claimed in any one or more of those claims. Indeed, Applicants may pursue claims of equal, lesser, or broader scope in one or more continuing applications.

Claim 1 has been amended to claim an embodiment of a method in accordance with the instant invention in which the presence of a target nucleotide on a nucleic acid is determined in a biological sample selected from blood, stool or urine. The support for this amendment can be found throughout the specification as filed, and in particular at page 6, lines 26-28, page 13, lines 21-22, as well as in claims 16 and 17, as originally filed.

Claim 10 has been amended to correct a typographical error.

Claim 19 has been amended to depend from claim 18 instead of claim 15.

Finally, new claims 25-27 have been added. Claim 25 is drawn to an embodiment of a method in accordance with the instant invention in which the presence of a nucleotide on a nucleic acid is determined in a biological sample comprising a bodily fluid. Dependent claim 26 is drawn to the method of claim 25, wherein the bodily fluid is selected from pus, semen, sputum, saliva, cerebrospinal fluid, biopsy tissue and lymph. Dependent claim 27 is drawn to a method of claim 1 or claim 25, comprising a pooled biological sample. New claims 25, 26 and 27 are supported throughout the specification as filed and in particular at page 6, lines 8-11, lines 13-15 and lines 26-28, as well as claims 16, 22 and 23, as originally filed.

Attached is a marked-up copy of the amended claims, as well as a clean copy of the complete set of pending claims as amended. No new matter is introduced by those amendments.

Remarks

Claims 1, 4, 10-12, 15-20 and 22-24 were considered in the Office action of September 28, 2001. Certain of the claims were rejected under 35 U.S.C. §§ 112, 102 and/or 103. Applicants amend claims 1, 10 and 19 and add new claims 25-27 herein. Applicants also cancel claims 16, 17, 22 and 23 without prejudice. Accordingly, after

entry of this Amendment and Response, claims 1, 4, 10-12, 15, 18-20 and 24-27 will be pending for examination. Applicants submit that the amendments and new claims introduce no new matter and that claims 1, 4, 10-12, 15, 18-20 and 24-27 are in condition for allowance.

Applicants respectfully request reconsideration and withdrawal of the rejections in light of the amendments and following remarks.

A. The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 10 was rejected under 35 U.S.C § 112, second paragraph. Specifically, claim 10 was said to be indefinite in the recitation of an improper Markush format for using the language "selected from the group consisting of A, B, C or D," instead of the language "...A, B, C and D."

Applicants amend claim 10 to recite "...group consisting of 6-carboxyfluorescein (FAM), 6-carboxy-X-rhodamine (REG), N_1, N_1 N^1, N^1-tetramethyl-6-carboxyrhodamine (TAMARA), 6-carboxy-X-rhodomine (ROX), fluorescein, Cy5® and LightCycler-Red 640." Applicants submit that amended claim 10 is now in a proper Markush format. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. The Rejection Under 35 U.S.C. § 102(a)

Claims 1, 4, 10, 12, 15, 16, 18, 20 and 24 were rejected under 35 U.S.C. § 102(a) as being anticipated by U.S. Patent No. 5,945,283 to Kwok et al ("Kwok").

In order for a prior art reference to anticipate the claimed invention under 35 U.S.C. § 102, the prior art reference must teach all of the claim limitations of the claimed invention. See *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (For a prior art reference to anticipate in terms of 35 U.S.C. 102, every element of the claimed invention must be identically shown in a single reference . . .").

Claim 1, as amended, recites a method for determining the presence of a target nucleotide on a nucleic acid in a biological sample that includes *blood, stool or urine* using a primer that has a covalently-attached donor molecule, and a dideoxy nucleotide

which has an acceptor molecule which is covalently-attached to the dideoxy nucleotide and will be incorporated into a primer extension product, and activated by fluorescent energy transfer from the donor molecule in accordance with the Applicants' claimed invention.

Kwok reports a method for determining the presence of a target nucleotide by adding to a *DNA sample* a primer covalently labeled with a fluorescent dye and performing primer extension in presence of a dideoxy nucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxy nucleotide is incorporated into the extension product. Kwok fails to disclose a method for detection of a nucleotide on a nucleic acid in a biological sample of *blood, stool or urine.* In fact, it is noted by the Examiner at page 6 of the Office action that Kwok entirely fails to disclose a method for detection of a nucleotide on a nucleic acid in a stool sample.

Because Kwok does not include all the limitations of the claimed invention, Kwok does not anticipate the claimed invention, as in amended claim 1. Claims 4, 10, 12, 15, 16, 18, 20 and 24 depend directly or indirectly from claim 1, therefore, are also not anticipated by Kwok.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C § 102(a) be reconsidered and withdrawn.

C. The Rejections Under 35 U.S.C. § 103(a)

Claims 11 was rejected under 35 U.S.C. § 103(a) over Kwok in view of U.S. Patent No. 5,945,526 to Lee et al. ("Lee"). Claim 19 was rejected under 35 U.S.C. § 103(a) over Kwok in view of Lu et al. (Chinese Medical Journal Abstract (1995)) ("Lu"). Claim 22 was rejected under 35 U.S.C. § 103(a) Kwok in view of O'Dell et al. (Clin. Chem. (1998) 44(1): 183-185) ("O'Dell"). Claims 17 and 23 were rejected over Kwok in view of U.S. Patent No. 5,483,834 to Gillespie ("Gillespie").

In order to establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art references and the motivation to combine the teachings of the references must be found in the references. See *In re Vaeck*, 947 F.2d

488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants address the rejections below in as much as it may apply to the claims as amended.

Kwok reports a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye and performing primer extension.....target nucleotide. As amended, each of the pending claims recite detecting a nucleotide on a nucleic acid in a biological sample selected from blood, stool or urine. Kwok entirely fails to teach use of a biological sample selected from blood, stool or urine, using a method of the claimed invention. None of Lee, Lu, O'Dell or Gillespie supply that missing element.

Lee teaches labeling dideoxy nucleotides with fluorophores, including 6-carboxyfluorescein, for use in energy transfer reactions. Lu teaches detection of mutations in the p53, apc and ras genes. O'Dell teaches a method of detecting mutations by screening pooled DNA samples. None of Lee, Lu or O'Dell alone or in combination with Kwok, teach or suggest a biological sample set forth in the claim as amended.

Regarding Gillespie, which is relied upon in the Office action for teaching performing an assay on a stool sample, Applicants note that Gillespie in fact teaches away from combining it with Kwok so as to modify the disclosure of Kwok to produce Applicants' invention. Gillespie recites at column 13, lines 11-19, "*...Clinical samples are commonly termed "dirty" when compared to research laboratory samples because of the high levels of impurities in such samples as stools, blood, urine, etc. The present invention has been tested across the spectrum of clinical samples and found to operate efficiently in all cases. The inventor is aware neither of prior art achieving this versatility nor of prior art anticipating this versatility. It was quite unexpected to the inventor.*" As such, Gillespie reports that assaying nucleic acids in biological samples such as stool, blood and urine is difficult and therefore, Gillespie teaches away from modifying the teachings of Kwok to produce Applicants' invention.

Accordingly, Applicants submit that Kwok even if combined with Lu, Lee and O'Dell does not teach or suggest all the elements of the claimed invention and furthermore, that Kwok and Gillespie are improperly combined. As such, Applicants

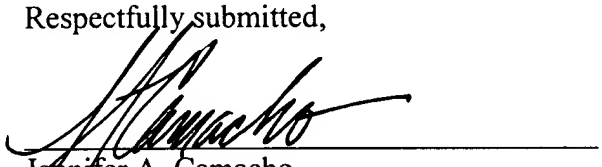
respectfully request that the rejection of the pending claims under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Based on the above amendments and remarks, Applicants respectfully submit that pending claims 1, 4, 10-12, 15, 18-20 and 24-27 are in condition for allowance and request entry as such. Applicants believe that no fee is due at the time of submission of this paper, however, in the event that any fees are due, the Director is hereby authorized to charge any such fees to Attorney's Deposit Account No. 20-0531.

If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at the telephone number below.

Respectfully submitted,



Jennifer A. Camacho
Attorney for Applicants
Reg. No. 43,526

Date: December 19, 2001
Testa, Hurwitz & Thibeault, LLP
125 High Street
Boston, MA 02110
(617) 248-7476

2243123

USSN 09/448,042

Amended Claims in Mark-Up Format

1. (Twice Amended) A method for determining the presence of a target nucleotide, the method comprising the steps of:

(a) exposing a biological sample selected from the group consisting of blood, stool and urine to a nucleic acid primer capable of hybridizing with a nucleic acid, said primer having a covalently-attached donor molecule comprising a fluorophore or a fluorescent dye;

(b) performing a primer extension reaction in the presence of a dideoxy nucleotide complementary to the target nucleotide, said dideoxy nucleotide having a covalently-attached acceptor molecule comprising a fluorophore or a fluorescent dye, said acceptor molecule being capable of being activated through fluorescent energy transfer from said donor molecule so as to produce a detectable fluorescent signal when said dideoxy nucleotide is incorporated into a product resulting from the primer extension reaction;

(c) determining the presence of said fluorescent signal, said presence being indicative of incorporation of said dideoxy nucleotide into the primer extension product; and

(d) determining the presence of said target nucleotide as indicated by the incorporation of said dideoxy nucleotide into the primer extension product.

10. (Twice Amended) The method of claim 1, wherein said fluorescent dye is selected from the group consisting of 6-carboxyfluorescein (FAM), 6-carboxy-X-rhodamine (REG), N_1, N_1 N^1, N^1-tetramethyl-6-carboxyrhodamine (TAMARA), 6-carboxy-X-rhodomine (ROX), fluorescein, Cy5® and [or] LightCycler-Red 640.

19. (Amended) The method of claim 18 [15], wherein said mutation occurs in a gene selected from the group consisting of ras oncogenes, p53, dcc, apc, mcc and β-catenin.

25. (New) A method for determining the presence of a target nucleotide, the method comprising the steps of:

(a) exposing a biological sample comprising a bodily fluid to a nucleic acid primer capable of hybridizing with a nucleic acid, said primer having a covalently-attached donor molecule comprising a fluorophore or a fluorescent dye;

(b) performing a primer extension reaction in the presence of a dideoxy nucleotide complementary to the target nucleotide, said dideoxy nucleotide having a covalently-attached acceptor molecule comprising a fluorophore or a fluorescent dye, said acceptor molecule being capable of being activated through fluorescent energy transfer from said donor molecule so as to produce a detectable fluorescent signal when said dideoxy nucleotide is incorporated into a product resulting from the primer extension reaction;

(c) determining the presence of said fluorescent signal, said presence being indicative of incorporation of said dideoxy nucleotide into the primer extension product; and

(d) determining the presence of said target nucleotide as indicated by the incorporation of said dideoxy nucleotide into the primer extension product.

26. (New) The method of claim 25, wherein said bodily fluid is selected from the group consisting of pus, semen, sputum, saliva, cerebrospinal fluid, biopsy tissue and lymph.

27. (New) The method of claims 1 or 25, wherein said biological sample is obtained from a pooled patient population.